CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206334Orig1s000

OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	John Farley, M.D.,M.P.H.
Subject	Deputy Office Director Decisional Memo
NDA #	206,334
Applicant Name	The Medicines Company
Date of Submission	December 6, 2013
PDUFA Goal Date	August 6, 2014
Proprietary Name / Established (USAN) Name	ORBACTIV Oritavancin diphosphate for injection
Dosage Forms / Strength	Sterile lyophilized powder, 400 mg oritavancin/vial
Proposed Indication	Acute Bacterial Skin and Skin Structure Infections
Action:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Mayurika Ghosh, M.D.
Statistical Review	Mushfiqur Rashid, Ph.D.
Pharmacology Toxicology Review	Amy Nostrandt, Ph.D., D.V.M.
CMC Review	Hitesh Shroff, Ph.D., Vinayak Pawar, Ph.D., Houda Mahyani, Ph.D.
Microbiology Review	Avery Goodwin, Ph.D.
Clinical Pharmacology Review	Ryan Owen, Ph.D.
Labeling Reviews	Justine Harris, RPh., Carrie Newcomer, Pharm.D.
DRISK Review	Suzanne Robottom, Pharm.D.
CDTL Review	Yuliya Yasinskaya, M.D.
Deputy Div. Director Review	Katherine Laessig, M.D.

OND=Office of New Drugs
CMC= Chemistry, Manufacturing, and Controls
CDTL=Cross-Discipline Team Leader
DRISK=Division of Risk Management

1. Introduction

Oritavancin is a lipoglycopeptide antibacterial, obtained by [redacted] (b) (4) of a fermentation product from *Kibdelosporangium aridum*, with in vitro antibacterial activity against certain Gram-positive bacteria. The drug product is manufactured as a lyophilized powder for injection. The mechanism of action is similar to that of the glycopeptide, vancomycin. The applicant has submitted NDA 206,334 for oritavancin diphosphate for injection for the indication of treatment of acute bacterial skin and skin structure infections (ABSSSI). After reconstitution, oritavancin is administered by intravenous infusion over 3 hours as a single 1200 mg dose. The proprietary name is ORBACTIV.

The efficacy review for this NDA relies upon the results of two adequate and well-controlled phase 3 studies (SOLO 1 and SOLO 2) evaluating the safety and efficacy of a single 1200-mg intravenous dose of oritavancin compared to intravenous vancomycin for the treatment of ABSSSI.

The review team has reviewed issues pertinent to their respective disciplines with regard to the safety and efficacy of oritavancin for the indication proposed. For a detailed discussion of NDA 206,334, the reader is referred to individual discipline specific reviews, the Cross-Discipline Team Leader (CDTL) Review, and the Deputy Division Director Review.

2. Background/Regulatory

NDA 22,153 was submitted in February 2008 by Targanta Therapeutics Corp. seeking approval of oritavancin for the treatment of complicated skin and skin structure infections. The proposed dose of oritavancin was 200 mg daily for 3-7 days. A Complete Response letter was issued on December 8, 2008 for NDA 22,153, citing efficacy and safety concerns. One of the Phase 3 trials did not demonstrate non-inferiority of oritavancin to vancomycin. While the second Phase 3 trial did demonstrate non-inferiority (NI), oritavancin did not appear to perform well in patients with infections caused by methicillin-resistant *Staphylococcus aureus*. In addition, there were a greater number of oritavancin-treated subjects with study drug discontinuation for lack of efficacy, serious adverse events of sepsis, septic shock, and related events, and adverse events of osteomyelitis and sepsis. Eosinophilic granules were noted in macrophages in animal studies, and further evaluation of macrophage function was recommended.

Following the Complete Response action for NDA 22,153, The Medicines Company assumed ownership of oritavancin and met with the Division on a number of occasions to discuss the development of oritavancin for the treatment of ABSSSI with the single 1200 mg dose regimen. Two new Phase 3 trials were planned. A Special Protocol Assessment agreement for the design of these two identical trials was issued on November, 24, 2010.

Throughout the period that oritavancin was under development with the single 1200 mg dose, there was considerable public discussion regarding the design of NI trials for serious bacterial infections including ABSSSI, particularly the primary endpoints for

which a NI margin could be justified. In 2010, FDA issued a draft Guidance entitled, *Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment*. The draft Guidance recommended a primary efficacy endpoint of clinical response (cessation of spread of lesion, and the absence of fever) at 48 to 72 hours for NI trials in ABSSSI. The SOLO 1 and SOLO 2 trials were designed with primary endpoints consistent with this recommendation. Following further public discussion, including input from the Foundation for the National Institutes of Health Biomarkers Consortium, a final Guidance was published October 16, 2013[1]. The final Guidance recommended a primary endpoint of ≥20% reduction in lesion size from baseline (no fever component) at 48-72 hours. Evaluation of this endpoint was a pre-planned sensitivity analysis in the SOLO 1 and SOLO 2 trials.

On October 31, 2013, The Medicine Company's oritavancin product for IV use was designated as a Qualified Infectious Disease Product (QIDP) for the following indication: treatment of ABSSSI. The NDA received a priority review.

3. Chemistry Manufacturing and Controls / Product Quality Microbiology

The Chemistry Reviewer concluded that the CMC information in the NDA was sufficient to assure the identity, strength, purity, and quality of the drug product.

The Product Quality Microbiology Reviewer concluded that there were no deficiencies and recommended approval.

An overall "Acceptable" recommendation for the manufacturing facilities for this NDA was made by the Office of Compliance.

The proposed 36 months expiration dating period, when stored at room temperature, is supported by the long-term stability and accelerated stability data.

I concur that there are no outstanding CMC issues that preclude approval.

4. Non-Clinical Pharmacology Toxicology

The Pharmacology Toxicology Reviewer did not identify any Pharmacology Toxicology concerns precluding approval.

Studies of toxicity in rats and dogs were reviewed at the time of the review of NDA 22-153, which proposed a clinical dose of 200 mg daily. Toxicities were similar with both species showing decreases in red blood cells, increases in BUN, AST/ALT, and histiocytosis with eosinophilic granules in liver, kidney, spleen, injection site, and lymph nodes. Due to these observations, the Complete Response letter for NDA 22-153 had

[1] Available at: http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185.pdf

recommended that a study assess macrophage function. In the current NDA, the applicant provided the results of in-vitro studies using murine J774 macrophages and differentiated human THP-1 cells, evaluating phagocytosis of latex beads, phagocytosis of bacteria, endocytosis of dextran, lysosomal integrity, and generation of reactive oxygen species. Based upon expected cellular concentrations of oritavancin in alveolar macrophages and results of the in-vitro studies, it is reasonable to conclude that effects on innate macrophage function would be unlikely to occur following treatment with a single 1200 mg dose of oritavancin.

No mutagenic or clastogenic potential for oritavancin was found in a battery of tests. Carcinogenicity studies were not performed due to the short duration of clinical use.

The applicant submitted new animal studies intended to qualify impurities and evaluate fertility. Single doses administered by IV bolus or infusion over 1 hour were associated with lethality in animals at doses lower than the proposed clinical dose of a single 1200 mg dose of oritavancin. Thus, safety of the proposed clinical dose has not been demonstrated in non-clinical studies. The Reviewer noted that development has proceeded based on safety determined in clinical trials.

The potential for reproductive toxicity was studied in rats and rabbits. The applicant proposed labeling the Pregnancy Category as (b) (4) As described above, the highest dose in the reproduction studies in rats and rabbits was approximately 25% of the clinical dose. The Reviewer recommended that Pregnancy Category C would be more appropriate, and I concur with this recommendation.

I conclude that there are no Pharmacology Toxicology issues that preclude approval.

5. Clinical Pharmacology

The Clinical Pharmacology Reviewer found the NDA acceptable from a clinical pharmacology perspective.

The applicant submitted a healthy volunteer pharmaco-kinetic (PK) study of the proposed 1200 mg single dose regimen. The Reviewer concluded that the proposed dosing regimen is supported by this study, but noted that there were some differences in oritavancin pharmacokinetics between healthy volunteers and patients. Based on population PK data from the SOLO 1 and SOLO 2 trials, the half-life was about twice as long in patients compared with healthy volunteers, which may have been due in part to differences in sample collection. (mean $t_{1/2}$ healthy volunteers- 120 hrs, SOLO 1- 244 hrs, SOLO 2- 245 hrs). $C_{max,}$ AUC, and CL differed, resulting in lower exposures and higher clearance in patients compared with healthy volunteers. Based on population PK modeling, the Reviewer concluded that no dose adjustments were necessary based on sex, age, race, body weight, or renal function.

The applicant conducted a study to evaluate the impact of oritavancin on the PK of probe drugs for several CYP450 enzymes as well as enzymatic activity studies. Oritavancin

was shown to be a weak inhibitor of CYP2C19 and CYP2C9 and a weak inducer of CYP2D6 and CYP3A4, but the observed interactions were weak in magnitude. S-warfarin, which is metabolized by CYP2C9, had an increase in mean AUC of approximately 30%. This 30% increase in warfarin exposure may be clinically significant in certain patients since warfarin has a narrow therapeutic window. The applicant has agreed to a labeling statement in WARNINGS and PRECAUTIONS described further in Section 8 of this memo. In addition, post-marketing studies have been agreed to by the applicant to further evaluate warfarin PK in the presence of oritavancin.

A thorough QT study was conducted in healthy adults with a single supra-therapeutic dose of IV oritavancin (1600 mg). No significant QT_c prolongation effects were detected in the study.

The applicant submitted the results of a number of PK/pharmaco-dynamic (PD) target attainment analyses to support the proposed breakpoints, and the reviewer conducted a number of his own analyses. The antimicrobial activity of oritavancin correlated with ratio of the area under the concentration-time curve to minimal inhibitory concentration (AUC/MIC). The Reviewer concluded that the various analytic approaches supported the proposed breakpoints discussed in Section 6 of this memo.

I conclude that there are no outstanding Clinical Pharmacology issues which preclude approval.

6. Clinical Microbiology

The Clinical Microbiology Reviewer did not identify any Clinical Microbiology concerns precluding approval.

The Reviewer concluded that data from surveillance and in-vitro studies supported the *in-vitro* activity of oritavancin against *Staphylococcus aureus* (including methicillin-susceptible [MSSA] and methicillin–resistant [MRSA] isolates), various species of *Streptococcus*, *Enterococcus faecalis, and Enterococcus faecium*.

Based on serial passage studies, there is a potential for oritavancin resistance, but mechanisms of resistance were not studied.

Based upon patient isolates and clinical response data in the SOLO 1 and SOLO 2 trials, the Reviewer recommended that oritavancin be labeled as indicated for the treatment of ABSSSI caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including MSSA and MRSA isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus* anginosus group (includes *S. anginosus, S. intermedius*, and *S. constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible isolates only).

The Reviewer assessed surveillance data, animal model data, clinical response by pathogen in the SOLO 1 and SOLO 2 trials, and the PK/PD target attainment models. Based upon these data, the Reviewer recommended susceptibility interpretive criteria for Susceptible as follows: *Staphylococcus aureus* ≤ 0.12 mcg/mL, *Streptococcus* species included in the INDICATION statement ≤ 0.25 mcg/mL, *Enterococcus faecalis* (vancomycin susceptible isolates only) ≤ 0.12 mcg/mL. Due to the poor diffusion of oritavancin in agar, the applicant was unable to develop a disk diffusion assay adequate for susceptibility testing at the time of NDA submission.

The applicant has agreed to conduct a U.S. surveillance study for 5 years post-marketing to evaluate the development of resistance to oritavancin in the organisms listed in the INDICATIONS section of labeling.

I conclude that there are no Clinical Microbiology issues precluding approval.

7. Clinical/Statistical Efficacy

The Statistical Reviewer, Clinical Reviewer, CDTL, and Deputy Division Director all recommended approval, concurring that the results of the SOLO 1 and SOLO 2 trials provided sufficient evidence that a single 1200 mg dose of oritavancin is noninferior to 7-10 days of vancomycin (1 g or 15 mg/kg twice daily) for the treatment of ABSSSI in adults.

The SOLO 1 and SOLO 2 trials are global, multicenter, randomized, double-blind, active-controlled, parallel-group clinical trials in patients with a ABSSSI suspected or confirmed to be caused by a Gram-positive pathogen. The primary objective of the SOLO trials was to establish noninferiority of single-dose intravenous (IV) oritavancin compared with IV vancomycin given for 7 to 10 days. The primary efficacy endpoint was a composite endpoint defined as the cessation of spread or reduction in size of the baseline lesion, absence of fever, and no rescue antibiotic medication at the Early Clinical Evaluation (ECE) time point of 48 to 72 hours after study drug infusion. The primary analysis population was the modified intent-to-treat (mITT) population, which included all randomized patients who were treated. Both trials sought to enroll approximately 500 patients per arm.

The Reviewer's analyses found that responder rates for the primary endpoint were similar between oritavancin and the comparator groups: 82.3% [391/475] vs.78.9% [378/479], a 3.4% difference (95% CI:-1.6%, 8.4%) in the SOLO 1 trial and 80.1% [403/503] vs.82.9%[416/502], a -2.7% difference (95% CI: -7.5%, 2.0%) in the SOLO 2 trial. The prespecified NI margin of -10% was met.

The endpoint of ≥20% reduction in lesion size from baseline (no fever component) at 48-72 hours was a secondary endpoint in both trials. The Reviewer's analyses found that the percentage of patients with lesion size reduction ≥ 20% from baseline at 48-72 hours were similar between oritavancin and the comparator: 86.9%[413/475] vs.82.9%[397/479], a

4.1% difference (95% CI: -0.5%, 8.6%) in the SOLO 1 trial and 85.9 % [432/503]vs. 85.3%[428/502], a 0.6% difference (95% CI: -3.7%, 5.0%) in the SOLO 2 trial.

An analysis of mean lesion area over time showed similarity between the oritavancin and vancomycin treated groups. Missing data patterns were similar between treatment groups. Subgroup analyses showed consistency of treatment effect in the oritavancin and vancomycin groups for the primary endpoint evaluating gender, age, race, geographic region, infection type, presence of diabetes mellitus, and baseline pathogen MRSA compared with MSSA.

I conclude that substantial evidence of efficacy has been provided.

8. Safety

The Clinical Reviewer concluded that the data submitted demonstrated an overall similar safety profile for oritavancin and the comparator vancomycin. The CDTL and Deputy Division Director did not identify any safety issues which would preclude approval, but raised the issues of coagulation test interference and the oritavancin-warfarin drug interaction and the need to mitigate risks through appropriate labeling.

The overall safety database consisted of 3,017 oritavancin-treated subjects from 22 clinical trials. A total of 1,075 ABSSSI patients were treated with the 1200 mg single dose oritavancin regimen.

Among patients in the SOLO 1 and SOLO 2 trials, 2 patients in the oritavancin group and 3 in the vancomycin group died. The Clinical Reviewer concluded that none of the deaths appeared to be related to study drug.

The incidence of treatment emergent serious adverse events in the SOLO 1 and SOLO 2 trials was 55.3% in the oritavancin group and 56.9% in the vancomycin group. Of note, there were 4 patients in the oritavancin group diagnosed with osteomyelitis. The Clinical Reviewer evaluated these case histories and concluded that the cases may be related to lack of efficacy of the proposed oritavancin regimen in osteomyelitis or failure to diagnose osteomyelitis at screening. This information will be included in the WARNINGS AND PRECAUTIONS section of the prescribing information.

Although the frequency of liver function test elevation was balanced between treatment groups in the SOLO 1 and SOLO 2 trials, there was 1 patient in the oritavancin arm compared with none in the vancomycin arm with an increase in ALT from normal at baseline to >10x ULN. There were 18 patients in the oritavancin group and 14 subjects in the vancomycin group who exhibited an increase in ALT from normal baseline to 3-5 x ULN. There were 3 patients in the oritavancin group and 1 patient in the vancomycin group who exhibited an increase in total bilirubin from normal baseline to 1.5-2 x ULN. No patients met Hy's law criteria.

Oritavancin has been shown to artificially prolong aPTT for 48 hours and the PT and INR

for 24 hours by binding to and preventing action of the phospholipid reagents which activate coagulation in commonly used laboratory coagulation tests. This interaction is described in WARNINGS and PRECAUTIONS in labeling. This has clinical implications for patients who require frequent aPTT monitoring, such as patients being treated with intravenous unfractionated heparin sodium. After discussions, the applicant agreed to a CONTRAINDICATION statement in labeling, "Use of intravenous unfractionated heparin sodium is contraindicated for 48 hours after ORBACTIV administration because the activated partial thromboplastin time (aPTT) test results are expected to remain falsely elevated for approximately 48 hours after ORBACTIV administration." This is consistent with the CONTRAINDICATION statement in labeling for heparin sodium injection, which states, "The use of heparin sodium injection is contraindicated in patients in whom suitable blood coagulation tests (e.g. whole-blood clotting time, partial thromboplastin time) cannot be performed at appropriate intervals". The applicant has agreed to a post-marketing study to further evaluate the effects of a single 1200 mg dose of oritavancin on coagulation test results in healthy volunteers.

As described in Section 5 of this memo, co-administration of oritavancin and warfarin would be expected to result in higher exposure of warfarin, which may increase the risk of bleeding. In addition, due to the artificial PT prolongation, monitoring of the anticoagulant effect of warfarin would be unreliable up to 24 hours after an oritavancin dose. After discussion, the applicant agreed to labeling in WARNINGS AND PRECAUTIONS focused on the potential risk of bleeding with concomitant use of warfarin, including a statement, "Use ORBACTIV in patients on chronic warfarin therapy only when the benefits can be expected to outweigh the risk of bleeding". The applicant has agreed to two post-marketing studies to evaluate safety/clinical significance of the drug-drug interaction between oritavancin and warfarin in patients with ABSSSI and health volunteers.

The DRISK Reviewer recommended that a REMS was not necessary.

I conclude that, with appropriate labeling to mitigate the risks of unreliability of commonly used coagulation tests and the oritavancin-warfarin drug-drug interaction, there are no safety issues which preclude approval.

9. Advisory Committee Meeting

There were no safety, efficacy, or other issues identified requiring advisory committee input, so no advisory committee meeting was convened.

10. Pediatrics

The applicant's proposed pediatric plan was found acceptable by the Pediatric Research Committee. The applicant submitted the protocol on December 16, 2013 for the first required pediatric study, a phase 1, open label, dose-finding, pharmacokinetics, safety and tolerability study of a single-dose oritavancin infusion in children which will step down through 5 age cohorts. The second required pediatric study is a phase 2 evaluator

blinded, randomized (b) (4) and safety study of oritavancin enrolling approximately 300 patients stratified by 5 age categories.

11. Other Relevant Regulatory Issues

Four clinical sites were inspected and the clinical inspection summary found acceptable by the Office of Scientific Investigations.

There are no other unresolved relevant regulatory issues.

12. Labeling

The proprietary name, ORBACTIV, was found acceptable by DMEPA.

Labeling recommendations from DMEPA and OPDP were incorporated as appropriate.

Labeling to address the safety issues of short-term unreliability of coagulation tests, warfarin-oritavancin drug-drug interaction, and an imbalance in osteomyelitis cases is discussed in Section 8 of this memo.

13. Decision/Action/Risk Benefit Assessment

Regulatory action: Approval

Risk-benefit assessment:

I concur with the review team that the results of the SOLO 1 and SOLO 2 trials provide substantial evidence of the efficacy of the single 1200 mg intravenous dose of oritavancin for the treatment of ABSSSI, caused by susceptible isolates of the designated bacteria. The dosing regimen will provide a useful option for physicians and patients for the treatment of ABSSSI. The safety issues identified in the course of the review, short-term unreliability of coagulation tests, warfarin-oritavancin drug-drug interaction, and an imbalance in osteomyelitis cases, can be mitigated through appropriate labeling. There were no CMC, Pharmacology Toxicology, Clinical Pharmacology, or Clinical Microbiology issues identified which would preclude approval. Overall, the risk-benefit is positive.

Recommendations for Post-marketing Risk Evaluation and Mitigation Strategies: None

Recommendation for Post-marketing Requirements and Commitments:

> Conduct an open label, dose finding, pharmacokinetics, safety and tolerability study of ORBACTIV (oritavancin diphosphate) single dose infusion in pediatric subjects less than 18 years of age with suspected or confirmed bacterial infections.

Conduct a multicenter, evaluator-blind, randomized study to evaluate the safety and tolerability of single-dose IV ORBACTIV (oritavancin diphosphate) versus vancomycin for the treatment of pediatric subjects less than 18 years of age with ABSSSI.

Conduct a U.S. surveillance study for five years from the date of marketing ORBACTIV (oritavancin diphosphate) to determine if resistance to oritavancin has developed in those organisms specific to the indication in the label for ABSSSI.

Conduct an open label trial evaluating the safety of a single 1200 mg IV dose of oritavancin in patients on concomitant chronic warfarin therapy, being treated for ABSSSI.

Conduct an open-label trial to assess the clinical significance of the drug-drug interaction between a single 1200 mg IV dose of oritavancin and warfarin in healthy volunteers.

Conduct a single-center, open-label trial to evaluate the effects of a single 1200mg IV dose of oritavancin on the results of multiple coagulation tests in healthy volunteers.

Conduct a study to evaluate the effects of oritavancin on phospholipid and non-phospholipid based coagulation tests *in vitro*.

Exclusivity:

Oritavancin has been granted QIDP designation. Oritavancin will be approved for the treatment of ABSSSI, the same indication identified in the QIDP designation letter of October 31, 2013. Oritavancin has not previously received a 5-year GAIN exclusivity extension. Therefore, the NDA meets the criteria for the 5-year GAIN exclusivity extension under section 505E(a) of the Act.

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/s/

JOHN J FARLEY
08/06/2014